The application was objected to because it failed to comply with the 37 C.F.R. §1.821 through §1.825 for reasons set forth on the Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Claims 13, 14, 22-29, 37, 40, 50, 51 and 53 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. Claims 13 and 14 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. It is also noted that the references associated with PTO Form 1449 were not available to the examiner in the instant application or in the parent application (08/352,322) and could not be found. The examiner requested copies of all PTO Form 1449.

Support for new claims 54-64 is found throughout the specification and in the claims as originally filed. Claim amendments are for purposes of improved clarity or consistency of claim language unless otherwise noted. No claim amendment should be construed as an acquiescence in any ground of rejection.

Support for immunoglobulins 10C5 and 4D1 is found throughout the specification. Additional support can be found, for example, in the specification at page 244, lines 5-9. Support for the equilibrium association constants in claims 58 and 59 can be found in the claims as originally filed. Further support can be found, for example, in the specification at page 246, line 24 through page 247, line 20. Support for the specific nucleotides for the CDR regions in claims 62, 63 and 64 can be found in their respective sequence listings. Additional support for claims 62, 63, and 64 can be found, for example, in the specification at page 41, line 29, through page 42, line 15.

Applicants appreciate the Examiner's Interview with Examiners DeCleux and Saunders at the U.S. Patent and Trademark Office on January 18, 2001.

Applicants use the paragraph numbering in the Office Action in responding to the examiner's remarks.

Sequence Disclosures

6. The application was objected to because it failed to comply with the 37 C.F.R. §1.821 through §1.825 for reasons set forth on the Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicants submit herewith, courtesy copies of the following documents filed concurrently as separate papers: a paper copy of a substitute sequence listing and a Communication under 37 C.F.R. §1.821 through §1.825 and Amendment.

Therefore, Applicants believe the objection to the application is now rendered moot and respectfully request that the objection be withdrawn.

Rejections Under 35 U.S.C. §112, first paragraph

8. Claims 13 and 14 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. The rejection of claims 13 and 14 is mooted by the cancellation of claims 13 and 14 without prejudice. Claims 13 and 14 were canceled to expedite prosecution.

Therefore, the rejection of claims 13 and 14 under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement, should be withdrawn.

9. Claims 13, 14, 22-29, 37, 40, 50, 51 and 53 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. Specifically, the examiner stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The rejection of claims 13, 14, 22-29, 37, 40, 50, 51 and 53 is mooted by the cancellation of these claims without prejudice.

Applicants canceled 13, 14, 22-29, 37, 40, 50, 51 and 53 to expedite prosecution, rendering the rejection under 35 U.S.C. §112, second paragraph, moot. Therefore, the rejection of claims 13, 14, 22-29, 37, 40, 50, 51 and 53 under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement, should be withdrawn.

Rejections Under 35 U.S.C. §112, second paragraph

11. Claims 13 and 14 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Applicants canceled 13 and 14 to expedite prosecution, not to overcome any rejection based on prior art, rendering the rejection under 35 U.S.C. §112, second paragraph, moot.

Therefore, the rejection of claims 13 and 14 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite, should be withdrawn.

Informalities

13. The examiner noted that the references associated with PTO 1449 were not available to the examiner in the instant application or in the parent application (08/352,322), and

could not be found. The examiner respectfully requested that the documents listed on the PTO Form 1449 be sent to the examiner for consideration.

As instructed by Examiner DeCloux, Applicants have forwarded copies of these references under separate cover (via FedEx) to the examiner on Friday, March 9, 2001, c/o the 7th Floor Receptionist at The U.S. Patent and Trademark Office, Crystal Mall 1, 1911 South Clark Street, Arlington, VA 22202.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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Support for the amendment to Table 20, page 251, line 6, in the left-hand column header, can be found, *inter alia*, at page 250, lines 22 and 23, which state that Table 20 provides equilibrium constants for anti-CD4 mAbs presented in the scientific literature. Support for the amendment to claim 10, and for new claims 46 and 47, directed to transformed cells comprising a human Ig which binds a human antigen, can be found, *inter alia*, on pages 96 to 97, lines 30 to 38 and 1 to 33, respectively. Support for the amendment to claim 13 and new claims 50 and 51 may be found, *inter alia*, on pages 95 to 96, lines 22 to 37 and 1 to 29, respectively, and in Example 41, pages 252 to 257. Support for the amendment to claims 22 to 30, directed to gene segments, can be found, *inter alia*, on page 256, lines 15 to 33 and page 235, lines 16 to 20.

Support for new claims 31 to 40, and 50 and 51, directed to human immunoglobulins that bind to human CD4 with high affinity can be found, *inter alia*, in Example 40 at pages 248 to 252. Support for new claim 35, directed to isolated human immunoglobulin from a hybridoma selected from the clones 1E11.15, 6C1.10, 1G1.9, 6G5.1, 10C5.6, 2E4.2, 4D1.4, 7G2.2 1F8.2 and 1G2.10, may be found, *inter alia*, in Example 40 at pages 248 to 252 and Example 41, pages 252 to 257. Support for new claims 37 to 40 directed to isolated human immunoglobulins that specifically bind human CD4 can be found, *inter alia*, in Example 40, pages 248 to 252 and Table 18, 19 and 21. Support for new claims 41 to 49, directed to transformed cell lines, may be found, *inter alia*, at page 96, lines 30 to 33, and in Example 39, pages 241 to 248; Example 40, pages 248 to 252 and Tables 18, 19 and 21.

Status of the Claims

Claims 10 to 14 and 18 to 30 are pending in the present application. Claims 31 to 51 are newly added in the instant amendment. Claims 1 to 9 and 15 to 17 are withdrawn from further consideration as being drawn to a non-elected species. For the Examiner's convenience, the pending claims *after* entry of the instant amendment is attached as Appendix A.

The Restriction Requirement and Election of Group III

In an Office Action dated August 22, 1997, claims 1 to 30 were restricted to four groups. In a response dated December 22, 1997, Applicants elected Group III, claims 10 to 14 and 18 to 30, drawn to an immunoglobulin that specifically binds to human CD4, without traverse.

The Election Requirement: Reconsideration of the First Restriction Requirement

In an Office Action dated April 6, 1998, a new Examiner, presently the Examiner of Record, reconsidered the Restriction Requirement of August 22, 1997, and further required an election of species. The Detailed Action alleged that the application contains claims directed to patentably distinct species of the claimed invention directed to CD4-specific immunoglobulins and hybridomas.

The Election of Species: An Election of Species Including Limitations of Claim 22

In a response dated September 8, 1998, Applicants elected species "M", drawn to the limitations of claim 22.

Claims Directed to CD4-Specific Igs With Specific Sequences are Free of the Art

Claims 13, 14 and 23 to 30, drawn to human Igs comprising specific amino acid sequences, where the Igs specifically bind to human CD4, have been found to be free of the art.

In light of the Examiner's comment in paragraph 1[1] that claims directed to particular amino acids are free of the art, Applicants believe that claim 22 may have been mistakenly cited in the section 103 rejection (claim 22 cites a particular sequence, too). Thus, claim 22 also should be deemed free of the art.

Outstanding Rejections

Claims 10 to 14 and 22 to 30 stand rejected under 35 U.S.C. §112, first and second paragraphs. Claims 10 to 12 and 22 to 30 stand rejected under 35 U.S.C. §112, second paragraph. Claims 10 to 12 and 18 to 22 stand rejected under 35 U.S.C. §103(a). Applicants respectfully traverse all the outstanding objections to the specification and rejections of the claims.

Informal Issues

Substitute Pages Provided

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[1] Please see page 2 of the "Detailed Action" of the instant Office Action.

Applicants thank the Examiner for noting that Tables 1, 2, 4 and 7 on pages 132, 138, 146, and 149 may be difficult to read. Substitute pages are enclosed herein (Appendix B). The substitute Tables 1, 2, 4 and 7 are identical to those as filed and they contain no new matter.

Status Priority Documents Updated

Applicants thank the Examiner for noting that the status of the priority documents for this application on the first line of the specification needed to be updated. The instant amendment addresses this issue.

New Title

Applicants thank the Examiner for noting that the title of the application as filed may not reflect the elected invention. The instant amendment addresses this issue.

Abstract Amended

Applicants thank the Examiner for noting that the Abstract of the application as filed may not reflect the elected invention. The instant amendment addresses this issue.

Identification of SEQ ID NO:s in Specification

Applicants thank the Examiner for noting that the specification is required to identify the nucleotide and amino acid sequences with SEQ ID NO:s. An amendment addressing this issue will be filed under a separate cover.

Specification Amended to Correct Spelling and Indicate Trademarks

Applicants thank the Examiner for noting that the specification may need to be amended to correct inadvertent spelling errors and to indicate trademark designations where appropriate; such an amendment will be submitted before payment of the issue fee.

Issues under 35 U.S.C. §112

Antecedent Basis for Claim 22 as Filed

The specification has been objected to under 37 CFR §1.75(d)(1) as failing to provide proper antecedent basis for the subject matter of claim 22 as filed.

Claim 22 is directed to a human sequence immunoglobulin comprising a VH4-34 segment, a DXP'1 segment, a JH4 segment, and a heavy chain CDR3 region comprising the sequence DITMVRGPH (SEQ ID NO:63).

Claim 22 is described in the specification, *inter alia*, in Table 23, page 257, line 1, which describes a hybridoma clone 1E11 which produces a mAb comprising a VH4-34 segment, a DXP'1 segment, a JH4 segment, and a heavy chain CDR3 region comprising the sequence DITMVRGPH (SEQ ID NO:63).

As requested by the Examiner, Applicants note that express support for the particular amino acid sequence set forth by SEQ ID NO:63 in claim 22 first appears in the instant specification.

Rejection under 35 U.S.C. §112, first paragraph

Claimed Immunoglobulins Enabled in Specification as Filed

Claims 13 to 14 and 22 to 30 stand rejected and the specification is objected to under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not sufficiently enabled by the specification. Specifically, it is alleged that it is not clear from the disclosure as filed that the particular Igs comprising the claimed elements set forth in claims 13 to 14 and 22 to 30 (specific amino acid sequences) would have the property of binding (human) CD4. The Patent Office invites Applicant to provide objective evidence that the Igs comprising these particular elements (specific amino acid sequences) do bind CD4.

Claims 13 to 14 and 22 to 30 are enabled by the specification as filed, *inter alia*, in Examples 40 and 41, pages 248 to 252 and 252 to 257, respectively. In particular, on page 248, lines 34 to 38, Example 40 notes that cells from 10 individual hybridoma cell lines (1E11, 1G2, 6G5, 10C5, 1G1, 6C1, 2E4, 7G2, 1F8 and 4D1) that secrete human IgG kappa mAbs reactive with human CD4 were derived from JHD/JCKD/HC2/KCo5 transgenic mice. Objective evidence that these human IgG kappa mAbs bind human CD4 with high affinity is provided, *inter alia*, in Tables 17, 18, 19, and 21. On page 253, lines 5 to 37, Example 41 states that cells from five of these hybridoma cell lines (1E11, 1G2, 6G5, 10C5, and 4D1) were used to isolate RNA encoding each of the individual antibodies. The RNA was used as a substrate to synthesize cDNA, which was then used to amplify human Ig gamma and kappa transcript sequences by PCR using primers specific for human VH, Vkappa, Cgamma, and Ckappa. The amplified Ig heavy and kappa light chain sequences were cloned into bacterial plasmids and nucleotide sequences determined. Analysis of the sequences spanning the heavy chain VDJ and light chain VJ junctions revealed in-frame heavy and light chain transcripts for

each of the 5 clones. Nucleotide sequences for each of the ten functional transcripts are assigned the sequence ID NOs 1E11 gamma (SEQ ID NO:1); 1E11 kappa (SEQ ID NO:2); 1G2 gamma (SEQ ID NO:3); 1G2 kappa (SEQ ID NO:4); 6G5 gamma (SEQ ID NO:5); 6G5 kappa (SEQ ID NO:6); 10C5 gamma (SEQ ID NO:7); 10C5 kappa (SEQ ID NO:8); 4D1 gamma (SEQ ID NO:9); 4D1 kappa (SEQ ID NO:10); see Table 22.

Finally, it is noted (on page 256, lines 16 to 18) that analysis of these DNA sequences demonstrates that the 5 hybridoma clones represent descendants of 4 individual primary B cells. Table 23 (pages 256 to 257) shows the amino acid sequences derived for each of the ten CD4-binding CDR3 regions, and the assignments for germline gene segments incorporated into each of the genes encoding these transcripts. These CDR3 regions include SEQ ID NO:63 in clone 1E11 (*i.e.*, DITMVRGVPH) , SEQ ID NO:64 in clone 1G2 (*i.e.*, PANWNWYFVL), SEQ ID NO:65 in clone 6G5 (*i.e.*, VINWFDP), SEQ ID NO:66 in clone 4D1 (*i.e.*, DQLGLFDY), SEQ ID NO:67 in clone 1E11 (*i.e.*, QQYGSSPLT), SEQ ID NO:68 in clone 1G2 (*i.e.*, QQFISYPQLT), SEQ ID NO:69 in clone 6G5 (*i.e.*, QQANSFPYT), SEQ ID NO:70 in clone 4D1 (*i.e.*, QQYDSYPYT).

Accordingly, the specification as filed sufficiently describes and enables claims 13 to 14 and 22 to 30 to satisfy the requirements of section 112, first paragraph, including providing objective evidence that human sequence antibodies comprising these sequences can bind human CD4.

Rejection under 35 U.S.C. §112, first and second paragraphs

Claims 10 to 14 and 22 to 30 stand rejected under 35 U.S.C. §112, first and second paragraphs as allegedly containing subject matter which was not enabled and/or not particularly pointing out or distinctly claiming the invention.

The Terms "substantially the same sequence" and "substantially identical to an amino acid sequence"

The Patent Office alleges that recitation of the terms "substantially the same sequence" or "substantially identical to an amino acid sequence" renders the claims indefinite. The term "substantially the same sequence" is found in pending claim 10. The term "substantially identical to an amino acid sequence" is found in pending claim 13.

Applicants respectfully assert that these terms reasonably apprise those of skill in the art of the scope of the claims and that the specification as filed sufficiently enables the claimed invention to satisfy the requirements of section 112. However, the instant amendment also addresses this issue.

Rejection under 35 U.S.C. §112 second paragraph

Claims 10 to 14 and 22 to 30 stand rejected under 35 U.S.C. §112, second paragraphs as allegedly failing to particularly point out or distinctly claiming the invention.

The Term "Artificial Gene"

The Patent Office alleges that recitation of the term "artificial gene" renders the claims indefinite. In the pending claims this term is used in claim 10.

Applicants respectfully assert that this term reasonably apprises those of skill in the art of the scope the scope of the claims. The instant specification defines the term artificial gene, *inter alia*, on page 91, lines 12 to 20. However, the instant amendment also addresses this issue.

The Term "Segment"

The Patent Office alleges that recitation of the term "segment" renders the claims indefinite. In the pending claims this term is used in claims 22 to 30.

Applicants respectfully assert that because the term "segment" is described in the specification,[2] the claims reasonably apprises those of skill in the art of their scope.[3] The law is clear that if the claims, read in light of the specification, reasonably apprises those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more.[4] The amount of detail required to be included in claims depends on the particular invention and the prior art, and is

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[2] Please see page 256, lines 15 to 33 of the instant specification; see also page 235, lines 16 to 20.

[3] The legal standard for definiteness under section 112, second paragraph, is whether a claim reasonably apprises those of skill in the art of its scope. *In re Warmerdam*, 33 F.3d 1354,31 USPQ2d 1754, 1759 *(citing Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d at 1217, 18 USPQ2d at 1030).

[4] *North American Vaccine Inc. v. American Cyanamid Co.*, 7 F.3d 1571, 28 USPQ 1333, 1339 (Fed. Cir. 1993) (*citing Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir. 1985), *cert. dismissed*, 474 U.S. 976 (1985).

not to be viewed in the abstract but in conjunction with whether the specification is in compliance with the first paragraph of section 112.[5]

The term "segment" read in light of the specification reasonably apprises the skilled artisan of the scope of the claim. For example, on page 95, lines 6 to 18, the specification states that by comparing the sequence of a cloned nucleic acid with a published sequence of human immunoglobulin genes and cDNAs, one of skill will readily be able to determine, depending on the region sequenced, (i) the germline segment usage of the hybridoma immunoglobulin polypeptide (including the isotype of the heavy chain) and (ii) the sequence of the heavy and light chain variable regions, including sequences resulting from N-region addition and the process of somatic mutation. The specification further notes that these gene segment assignments are available from the National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, Bethesda, Md.

Accordingly, the term "segment" reasonably apprises the skilled artisan of the scope of the claim satisfying the requirement of section 112, second paragraph.

Issues under 35 U.S.C. §103(a)

Cobbold, et al. and Queen, et al.

Claims 10 to 12 and 18 to 22 stand rejected under 35 U.S.C. §103(a) as obvious over Cobbold et al., U.S. Patent No. 5,690,933, filed August 12, 1994, and Queen, et al., U.S. Patent No. 5,530,101, filed December 19, 1990.

As noted above, in light of the Examiner's comment in the instant Office Action (in paragraph 1) that claims directed to particular amino acids are free of the art, Applicants believe that claim 22 (itself directed to particular amino acids) may have been mistakenly cited in this section 103 rejection.

Support for Claims Directed to Human Sequence Igs Specific for Human Ags are Enabled by Priority Applications that Predate both Cobbold, et al. and Queen, et al.

Claims directed to human sequence immunoglobulins specific for human antigens are sufficiently enabled by priority applications USSN 07/574,748, filed August 29, 1990, and USSN 07/575,962, filed August 31, 1990, to satisfy the requirements of section 112.

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[5] *Shatterproof Glass Corp.*, 225 USPQ at 641.

Thus, the filing date for applications which support such claims predate the filing dates of both Cobbold, et al. and Queen, et al. Accordingly, neither Queen nor Cobbold are prior art to such claims.

Cobbold, et al., Filed Aug. 12, 1994, is Not Prior Art to the Claimed Invention

Cobbold et al., U.S. Patent No. 5,690,933, was filed August 12, 1994. However, the claimed invention can claim priority at least to the priority document USSN 08/053,131, filed April 26, 1993, issued as U.S. Patent No. 5,661,016 on August 26, 1997. In this priority document, support for generating human antibodies to human CD4 can be found, *inter alia*, in Example 26,[6] which describes immunization of transgenic mice (with both human heavy and κ light chain gene segments) with human CD4 to produce all human antibodies. See also Figure 48, which shows human antibody reactivity to human CD4 in an Ab/Ag capture assay.

See also priority document USSN 08/096,762, filed July 22, 1993, issued as U.S. Patent No. 5,814,318, on September 29, 1998, which describes the generation of human antibodies to human CD4 in, *inter alia,* Figure 55. Fig. 55 which shows the titers of antibodies comprising human μ, human γ, and human κ chains in human anti-CD4 antibodies found in the serum of immunized transgenic mice taken at three weeks or seven weeks post-immunization with human CD4. This data also shows that human γ chains are present at significantly increased abundance in the 7 week serum, indicating that cis-switching within the heavy chain transgene (isotype switching) is occurring in a temporal relationship similar to that of isotype switching in a wildtype animal.

See also priority document USSN 08/161,739, filed December 3, 1993, particularly Example 34, which describes, *inter alia*, generating human mAbs specific for human CD4 by generating and isolating hybridomas from transgenic mice homozygous for an inactivated endogenous Ig locus which have been reconstituted with human Ig transgenes. Example 34 demonstrates the ability to make human Ig directed to human CD4. Mice were immunized with cells expressing transfected human CD4. Supernatants of the isolated hybridomas were tested with soluble recombinant human CD4. The anti-CD4 monoclonal antibodies were found to be human κ- and μ-chain containing mAbs.

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[6] Page 139 to 140 of the priority document's specification.

See also priority document USSN 08/165,699, filed December 12, 1993, which describes, *inter alia*, that transgenic mice immunized with recombinant soluble human CD4 generate human antibodies to the rCD4 (see Fig. 71A and 71B).

See also priority document USSN 08/209,741, filed March 9, 1994, which describes, *inter alia*, the generation of human IgG and IgM to human CD4 in transgenic mice and the generation and isolation of a hybridoma expressing a fully human IgMκ anti-human CD4 mAb. See, e.g., Figure 72, which shows reactivity of the hu IgMκ anti-huCD4 mAb with freshly isolated human PBL. See also Figures 73 and 74, which show levels of hu IgMκ secretion by the hybridomas isolated from the transgenic mice.

These priority documents sufficiently describe and enable the claimed invention with respect to the generation of human antibodies to human CD4 in transgenic mice to satisfy the requirements of section 112, first paragraph. The filing date of these priority documents pre-date the filing date of Cobbold, et al. Accordingly, Cobbold, et al. is not prior art to the invention as set forth in claims 10 to 12 and 18 to 22.

A prima facie case of obviousness has not been established

Implicit in this rejection is that Cobbold, et al. or Queen, et al. contain deficiencies that are cured by the other. Applicants will show that the deficiencies of each cited patent are not cured by the other. Accordingly, a *prima facie* case of obviousness has not been established and the rejection should properly be withdrawn.

Cobbold et al. is relied on for allegedly teaching the generation of antibodies to CD4 from different species, including humans. It is acknowledged that Cobbold, et al. differs from the pending claims by not exemplifying such human or humanized CD4 specific antibodies or cells that comprise these antibodies.

Applicants respectfully assert that Cobbold et al. is defective because it not only does not exemplify any human CD4 specific antibodies it also does not describe any means to make any human sequence antibodies. Cobbold et al. teaches no means to make any human sequence antibodies. In fact, it was the solution to this long-felt need that was for the first time discovered and described by the instant inventors in this and the priority documents.

Queen, et al., is relied on for allegedly teaching the generation of recombinant or humanized antibodies. It is acknowledged that Queen, et al. differs from the instant claims by not exemplifying the particular human CD4 specificity for such antibodies.

Applicants respectfully assert that Queen, et al. is further defective in that it does not teach the generation of fully human antibodies. Instead, Queen, et al. teaches "humanized immunoglobulins" also known as "chimeric antibodies." Significantly, the antibodies taught by Queen, et al. contain mouse sequence. Because Queen, et al. did not even attempt to generate an all human antibody, they teach first generating mouse immunoglobulins against a human antigen, isolating the mouse sequence responsible for binding the human antigen, and thereafter splicing that mouse sequence into a human immunoglobulin structural framework to generate a chimeric mouse/human polypeptide. The presence of mouse sequence in the chimeric polypeptide may be a weakness because the mouse sequence may be antigenic when injected into humans. Thus, the patient may generate antibodies against the Queen, et al. chimeric antibody after repeated administration. The immunogenicity of the chimeric therapeutic antibody of Queen, et al.may limit its long-term use. Although chimeric monoclonal antibody immunogenicity may be reduced by limiting the number of foreign (*i.e.*, non-human, mouse) residues, these strategies do not prevent a response to the remaining mouse sequence following repeated administration. The instant invention, by generating fully human antibodies in transgenic mice without the requirement of additional engineering steps, has solved this problem.

Thus, Queen, et al. cannot cure the deficiency of Cobbold, et al., which does not teach how to generate a fully human antibody. Likewise, Cobbold, et al. cannot cure the deficiencies of Queen, et al.

Accordingly, a case of *prima facie* obviousness has not been established. Applicants respectfully submit that in view of the above presented arguments, the rejection of the claims under 35 U.S.C. §103 should be properly withdrawn.

CONCLUSION

In view of the foregoing remarks, it is believed that the Examiner should withdraw the objection to the specification and the rejection of the claims under 35 U.S.C. §112, first and second paragraphs, and 35 U.S.C. §103. Applicants believe all claims now

pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned or Bill Smith at 415-576-0200.

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